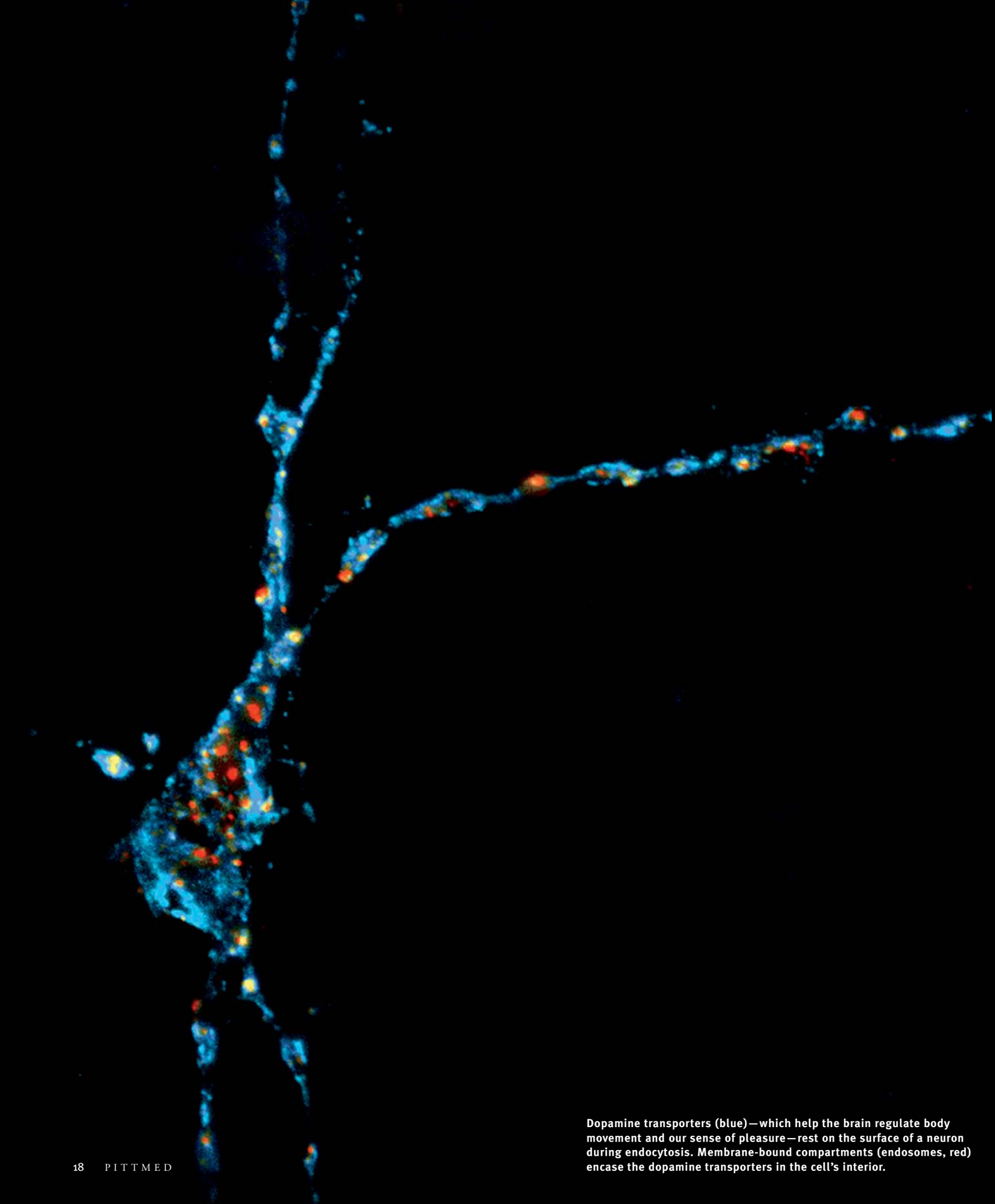

Dopamine transporters (blue)—which help the brain regulate body movement and our sense of pleasure—rest on the surface of a neuron during endocytosis. Membrane-bound compartments (endosomes, red) encase the dopamine transporters in the cell's interior.

ALEXANDER SORKIN STAKES OUT CANCER AND ADDICTION AT THE MOLECULAR LEVEL

BY ELAINE VITONE

TRAFFIC

Alexander "Sasha" Sorkin has spent decades staking out the comings and goings in our cells—how proteins enter them, how the cells usher in the good guys, how they shut down the bad guys before they can cause trouble. Biologists call this essential process—this busy movement of molecules—"membrane trafficking," and in a vague sense, the allusion to narcotics commerce seems apt. When molecular deals go south, cells can follow very dark paths, living fast and dying young.

Sorkin investigates two seemingly disparate cell types, following each of them from the first, minor infractions to the worst ends: epithelial cells to cancer (namely head and neck and lung cancers) and neurons to drug addiction. His gift is careful, basic science at its most fundamental level; but unlike many basic scientists, he's been known to partner with physicians and others who best know how to help those who are all too often caught in the cross fire when trafficking gets ugly: patients.

IMAGE | COURTESY ALEXANDER SORKIN

Previously a professor of pharmacology at the University of Colorado, Sorkin joined the Department of Cell Biology and Physiology as Richard B. Mellon Professor and Chair in March. He hopes to bring to his new leadership role the same passion for collaboration that he has fostered since his rookie days.

"We still need to do a lot of basic science," Sorkin says. "But it's time for us to also be direct contributors in diagnostics and drugs—to really improve outcomes for people."

Sorkin has curly, salt-and-pepper hair and speaks with the accent of his native Russia. His colleagues say he's a joy to work with, thoughtful and congenial—never competitive or aggressive. They call him adventurous and passionate, but cautiously so. He's not the type who hangs posters of his work outside his office, or even lets on that he's particularly jazzed about how things are turning out. For all of Sorkin's many accomplishments, he still walks into each new project making pronouncements like: *This will never work. I am sure that we are wrong. This will be a disaster.*

"Usually he says these things with a little bit of a chuckle," says Sorkin's longtime collaborator Mark Von Zastrow, professor of psychiatry and cellular and molecular pharmacology at the University of California, San Francisco. Von Zastrow suspects that at least part of that trademark-Sorkin pessimism is genuine—just enough to help him as a scientist.

"I think what it means is that he's willing to be self-critical."

CANCER'S "GROW HOUSE"

When Sorkin was a postdoc at Vanderbilt University in the early '90s, we were just beginning to understand the protein known as epidermal growth factor (EGF), which plays a vital role in cellular growth, reproduction, and differentiation. EGF is also thought to be an essential, driving force in a variety of cancers—patients who have higher levels of EGF in their tumors are more likely to die. (Nobel Prize-winner Stanley Cohen, of Vanderbilt, discovered EGF in 1972. Sorkin was mentored by Cohen's protégé, Graham Carpenter.)

EGF's receptor, EGFR, straddles the membrane of the cell. When EGF comes along, the two join, and EGFR "activates," sending a message to the nucleus: Grow. If too many active receptors are around, cells not only divide more than normal, they also stop dying as part of their natural course. This pattern gives rise to cancer.

The cell's defense against letting those extra, trouble-making receptors wreak havoc is to "traffic" them—or move them—inside the cellular membrane and into one of its lysosomes (the garbage incinerators of cells), then destroy them. But unfortunately, there are limits to how many excess receptors a cell can dispose of at a time. Ten to 20 thousand, no sweat. One or two million, however, and you've got yourself a problem.

EGFR is an approved therapeutic target for head and neck, lung, colon, and pancreatic cancers. Drugs along these lines treat cancer by cutting the EGFR count throughout the body as a whole. These therapies are far easier on the body than chemotherapy treatments, but they're not perfect. In rare cases, patients have significant side effects. Absent enough EGFRs, tissue that would normally stay healthy through constant cellular regeneration—like that in the intestines, skin, reproductive organs, and liver—can suffer. But more importantly, these drugs only help 10 to 12 percent of patients.

"This is not acceptable," Sorkin says.

He's developed cell lines to help him understand what separates the lucky 10 to 12 percent from the rest. His research is giving him a clearer picture of EGFR's partners in crime: i.e., the proteins—and the amino acids within them—that are involved in trafficking.

Sorkin believes EGF is a player in almost all cases of head and neck cancer and more than 50 percent of lung cancer cases. These are devastating diseases with very low cure rates. However, he believes that in time, it could be possible to save as many as half of these patients—but that depends on the quality of our intelligence-gathering. It's not enough to know EGFR is involved; we also have to find out when and how. For example, in some cancers, EGFR doesn't stir up trouble in the initial phase, but it does in metastasis, so in terms of treatment, timing is everything. In other cancers, EGFR is only a good target for patients with a certain genetic mutation.

Jennifer Rubin Grandis (MD '87, Fel '92, Res '93) has been friends with Sorkin for years, having served on several grant-reviewing panels with him. Grandis, who holds the UPMC Endowed Chair in Head and Neck Cancer Surgical Research and is a professor of otolaryngology and pharmacology in Pitt's School of Medicine, leads the Head and Neck Cancer Program at the University of Pittsburgh Cancer Institute. Sorkin says she's one of the reasons he decided to come to Pittsburgh. The two plan to collaborate once he's settled in.

"I think he's one of these rare basic scientists who is willing to step outside of his comfort zone," says Grandis. "In Colorado, he sought out collaborators—specifically, clinicians—who were caring for patients with cancers he was studying and trying to figure out how his work could ultimately benefit people with cancer.

"He's not afraid of saying, 'I don't understand that. Help me understand.'"

EAVESDROPPER

As any police detective knows (at least the ones on television), if you want to get a line on your perp's M.O., there's nothing like a wiretap. That's why, in addition to watching the busy molecular comings and goings of membrane trafficking, Sorkin is also eavesdropping. He's an expert in signaling—the process by which proteins communicate.

Scientists used to think that once a receptor passes through the cellular membrane—the first step on the way to the dumpster—it's incommunicado. In a paper published in *Current Biology* in 2000, Sorkin became the first to prove that this assumption was false.

Rather, Sorkin believes the cell's interior is where most EGFR signaling happens in head and neck cancer, and perhaps a significant amount happens there in the case of lung cancer, as well. Yet, many of the drugs that target EGFRs are only effective against the receptors on the outside of the cell.

Sorkin has used a microscopy technique called FRET (fluorescence resonance energy transfer), a method in which two proteins are marked with fluorescent tags of different colors. When the proteins come into close contact, you can excite the tag on one molecule and watch—in real time—as the energy transfers to the other molecule, causing it to fluoresce during signaling.

To get even more detailed data, Sorkin developed what he calls "Triple FRET," so that it's possible to witness this interaction between three molecules, rather than two. This imaging technique has been helpful for scientists in a wide range of research fields—from heart disease to cognitive studies. Sorkin's colleagues call this feat of ingenuity the work of a triple-threat investigator.

"Sasha is a very insightful and creative scientist," says Carpenter, Sorkin's mentor. "He has a broad range of skills. Some people are trained biologists and have trouble getting into chemistry or math. He can do all three."

At Pitt, Sorkin aims to take trafficking models once again to a new level by develop-

COURTESY A. SORKIN

As a chair at Pitt, Sorkin—cell biologist and once-avid climber—will stretch himself beyond his comfort zone.

ing a dynamic, three-dimensional simulation that moves through both space and time. He's still in the data-gathering phase for now, but Sorkin hopes that once the new model is complete, it will allow his team to predict possible outcomes and decipher which therapies and combinations of therapies are worth pursuing. The project has been funded by a National Institutes of Health Grant in Health and Science Research as part of the American Recovery and Reinvestment Act of 2009.

Sorkin looks forward to eventually collaborating with Pitt's Simon Watkins, professor and vice chair of cell biology and physiology, professor of immunology, and director of the Center for Biologic Imaging. The feeling is mutual.

"I'm excited about Sasha's studies," Watkins says. "They have embraced the power of complex optical imaging in an elegant and functional way. It's a hybrid—very creative. He's using many, many methodologies—and even creating new ones—rather than just doing the same thing every time."

The new model will reveal not just movement from Point A to Point B to Point C, but when each stage of the sequence happens, and at what speeds.

"So it's 4-D," says Sorkin. "Well, if it's two proteins, that's more like 8-D. Well, anyway, we call it multidimensional microscopy."

THE DOPE ON DOPAMINE

Dopamine is a neurotransmitter, a chemical messenger in the brain associated with the pleasure system and body movement. It plays a role in both keeping us on an even keel and in neurological and psychiatric disorders.

The neuron's dopamine transporter protein is similar to the EGF receptor in that it's embedded in the cell surface, and it's responsible for cellular trash collection. (However, the dopamine transporter never sends any signals on its own.)

We used to think that the dopamine transporter remained stationary, embedded in the membrane. But in 1999, Pitt neurobiology chair Susan Amara (she was at Oregon Health and Science University at the time) became one of the first to demonstrate that the transporter can go inside and back—that it, too, is trafficked. It was a revelation in the field.

Amara also discovered exactly how cocaine and methamphetamine affect the brain at the cellular level—essentially, by latching onto the dopamine transporters and keeping them from doing their job. With the dopamine vacuum cleaners out of commission, dopamine runs amok, resulting in thoughts and movements on fast-forward.

By then, Sorkin was already an internationally recognized membrane-trafficking expert. He wondered how applying his knowhow to the world of dopamine-transporter trafficking might help people struggling with cocaine and methamphetamine addiction. There is no pharmaceutical treatment for people hooked on these narcotics, no way to ease the torturous journey back down to sobriety. Additionally, as a visual scientist, he found the highly complex terrain of the brain fascinating. Problem was, he didn't know anything about it.

As luck would have it, someone who did—a neuropharmacologist who was dying to learn more about the dopamine transporter—happened to be working just down the hall from him. That was Nancy Zahniser, professor and associate dean for research education in the University of Colorado School of Medicine. (She's also a '77 PhD graduate of Pitt's School of Pharmacy.)

"If you drew the two circles of our expertise and interests, there was this tiny little overlap," says Zahniser. "So that's how we got together." The two went on to collaborate for more than 10 years.

Many labs were working on dopamine-transporter research at the time, but Sorkin's trafficking expertise made him stand out. Together, Sorkin and Zahniser identified the enzyme NEDD4-2 as a component of dopamine-transporter trafficking. Zahniser is sad to see Sorkin go ("Pitt's gain is our loss," she says), but she's glad for him to be in his new home, rich with prospects for new collaborations with Amara and other top-notch dopamine investigators.

Dopamine transporters are notoriously sparse and difficult to pin down. Recently, Sorkin developed a mouse model with tags on its dopamine transporters that made them much easier to study. The project is funded by the National Institute on Drug Abuse. Zahniser is thrilled about what this new tool might mean for the broader field.

For example, eventually she hopes to use Sorkin's mouse to investigate differences in individual animals' responses to cocaine. She wonders: Are the animals that have higher numbers of dopamine transporters resistant to cocaine-induced changes in transporter trafficking? And if so, what does that mean? Would a more sluggish pace mean a more addiction-prone brain? And if so, then could the trafficking process be helped along somehow? Could we rescue people from the throes of addiction?

CLIFF HANGER

Back in the former Soviet Union, Sorkin competed with a speed-climbing team semi-professionally from 1975 to 1987 and has been an avid mountaineer since. He has seen the tops of Mont Blanc, Grand Teton, and several peaks along the Caucasus, Tian Shan, and Pamir ranges.

More recently, it's been harder to fit in as much climbing as he'd like; and since he's arrived in Pittsburgh, it's become harder still. When he was offered the job, leaving the mountains of Colorado was one of the hardest parts of his decision.

"When I climb," he says, "I forget everything else. I'd try to take papers to read in the tent when we'd go on those month-long expeditions, but in all my career, I could never read one page. I could read books, but not scientific papers. It was like I was rebooting my computer."

The Pitt appointment is Sorkin's first experience in administration. His move surprised his old friends—and even Sorkin himself—because he prefers to keep a low profile. But Sorkin saw this as another chance to stretch and grow, to leave his comfort zone. And besides, when Pitt's School of Medicine came courting, the promise of marrying basic science to clinical science on a grander scale won him over. Apparently, some adventures are even more irresistible than cresting a mountain. "In science, you're always learning something new," he says, "something that no one in the human race has ever known. It's like discovering a new island. It might be a small island, but it's new." ■